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Research Article

Clinical Utility of a Novel Test to Diagnose Alzheimer's Disease in Patients with Suspected Dementia

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Abstract

Background: Historically, Alzheimer's Disease (AD) diagnosis has been made using non-specific tests (imaging and/or CSF biomarkers). The DISCERN™ test is a novel AD test combining three biomarkers: Morphometric Imaging, Protein Kinase C ε, and AD-Index, and is validated against autopsy confirmed diagnosis (NIH gold standard for AD diagnosis) with 95% sensitivity and 95% specificity.

Materials and Methods: We utilized a web-based survey to estimate treatment decisions from a sample of primary care physicians (PCPs), neurologists, and geriatricians. Computer software was used to randomly generate hypothetical patient profiles with five attributes: MRI/CT Scan results, MMSE score, Blood test results (TSH, Vitamin B12, Folate, Syphilis, Lyme disease), Age, and DISCERN™ result. Each physician viewed 7 of 27 unique profiles generated, using a least-fill methodology. For each profile, physicians indicated whether they would diagnose the patient with AD, prescribe medications indicated to treat AD symptoms, refer the patient to a neurologist (PCPs and geriatricians only), and prescribe a futuristic disease-modifying drug (Drug X). Aggregate logit models were used to assess attribute importance.

Findings: 402 physicians participated in the survey (250 PCPs, 102 neurologists, and 50 geriatricians). 4% of physicians expressed satisfaction with current tests, and 90% indicated they were likely to order DISCERN™. DISCERN™ result was the most important attribute in most physician decision-making scenarios; physicians were more likely to diagnose AD with a positive DISCERN™ result vs no test (relative attribute importance (RAI):64%; OR: 6.45; 95% CI: 5.09-8.17). A positive DISCERN™ result was associated with significantly higher odds of prescribing Drug X (RAI: 62%; OR: 4.12; 95% CI: 3.36-5.04) and prescribing treatments for AD symptoms (RAI: 54%; OR: 2.98; 95% CI: 2.40-3.68). Physicians were significantly less likely to prescribe treatments with a negative DISCERN™ result vs no test (OR: 0.58; 95% CI: 0.48-0.70).

Conclusions: This study indicates that DISCERN™ test results have a significant impact on physician decision-making regarding AD diagnosis and management.

ABBREVIATIONS

AD: Alzheimer's Disease; CLIA: Clinical Laboratory Improvement Amendments; CSF: Cerebrospinal Fluid; CT: Computed Tomography; CVA: Conjoint Value Analysis; IRB: Institutional Review Board; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MRI: Magnetic Resonance Imaging; NIH: National Institutes of Health; PCP: Primary Care Physician; PET: Positron Emission Tomography; RAI: Relative Attribute Importance

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease with a complex and multifaceted pathology. Several factors including genetics, lifestyle, and environmental factors are known to impact the risk of AD [1]. AD is the most common cause of dementia, accounting for 60-80% of cases. The 2021 Alzheimer's Association Report estimates 6.2 million Americans ages 65 and older currently have AD [2]. In 2019, a total of 121,499 deaths were recorded from AD, making it the sixth leading cause of death among all Americans. Dementia imposes a substantial disease burden on patients and caregivers. The 2021 Alzheimer's Association Report also estimates 15.3 billion caregiver hours spent in the care of patients with AD or other dementias [2]. The indirect cost burden of dementia in 2020 was estimated at $256.7 billion, while direct payments (including healthcare, long-term care and hospice) are estimated at $355 billion in 2021.

Currently, there is no single, definitive modality for AD diagnosis. The current standard of care (SOC) tests used to diagnose dementia incorporate different tools that, when used together, can presumptively diagnose AD by excluding other causes of dementia (Table 1).

Table 1: Current Diagnostics Used in The Patient Journey for Alzheimer's Disease.

Test Type	Test	Application
Personal/Medical History	Foundational Workup	Generic evaluation of health
	Neurological Examination	Generic evaluation of cognition
	Psychiatric Evaluation	Generic evaluation of psychiatric health
Cognitive Testing	MMSE	Assessment of neurocognitive abilities
	Mini-Cog	Assessment of neurocognitive abilities
	MoCA	Assessment of neurocognitive abilities
Blood Testing	TSH	Rule out other causes of memory loss
	Vitamin B12	Rule out other causes of memory loss
	Folate	Rule out other causes of memory loss
	Syphilis/Lyme Disease	Rule out other causes of memory loss
Brain Imaging	CT	Assess for microhemorrhages, cerebral amyloid angiopathy or atrophy
	MRI	Assess for microhemorrhages, cerebral amyloid angiopathy or atrophy
	PET	Assess for microhemorrhages, cerebral amyloid angiopathy or atrophy, and amyloid-β plaque and tau tangle deposition
Biomarker Testing	CSF, blood test	Evidence of tau and beta amyloid deposition

Patients suspected of having AD-dementia are prescribed medications to improve cognitive impairment including acetylcholinesterase inhibitors (e.g., galantamine, rivastigmine, and donepezil) and NMDA inhibitors (i.e., memantine). In June 2021, the Food and Drug Administration (FDA) approved aducanumab (Aduhelm™), a disease-modifying drug for the treatment of patients' earlier stage AD [3]. Depending on the severity of AD perceived by the physician, primary care physicians (PCPs) may refer patients to neurologists for further management post-diagnosis [4].

There are several unmet needs and challenges with current AD diagnostic tools for a patient with suspected dementia. First, currently available AD diagnostics are not accurate with sensitivity and specificity ranging from 70.9% to 87.3% and 44.3% to 70.8%, respectively, indicating that many AD diagnoses may be dementia of another etiology, possibly one that can be treated [5]. Second, there is no single test that can definitively diagnose AD and distinguish it from other forms of dementia. Existing tests are subjective in nature; results and interpretation are impacted by age, education, ethnicity, and other sociodemographic factors [6,7]. As a result, clinicians are compelled to discuss limitations of current tests when discussing results with patients and caregivers [8]. Current blood chemistry tests rule out other causes of memory loss; imaging tests, including MRI and CT scans, can identify other pathology associated with dementia symptoms (e.g., vascular, Lewy body dementia), but cannot definitively rule in or rule out AD or mixed dementia; PET scans can detect amyloid-β plaques and tau tangles, which are associated with AD, but PET scans themselves are not diagnostic and are inaccessible due to costs and limited coverage. The current diagnostic pathway may not only lead to frustration and anxiety for patients and family members, but may also negatively impact patient management, as a more definitive diagnosis could help physicians prescribe treatments, provide care, and enable enrollment in clinical trials. Lastly, the U.S. National Institutes of Health (NIH) "Gold Standard" for diagnosing AD objectively involves detecting presence of dementia in life combined with testing for beta-amyloid and tau protein deposition at autopsy [5]. However, detection of amyloid plaques and tangles upon imaging, invasive CSF testing, or blood testing does not mean a patient has AD and these tests are therefore not diagnostic [9,10].

The DISCERN™ test was developed as an objective and accurate test for identifying early-stage AD (within 4 years of a diagnosis of dementia) and distinguishing AD from other forms of dementia. It is intended for use by neurologists, PCPs, and geriatricians in patients ages 55-90 years old with suspected dementia. The DISCERN™ test is comprised of three assays that assess several critical factors directly related to AD that regulate memory, the formation of synaptic connections among neurons, and the levels of amyloid plaques and levels of neurofibrillary tangles in the brain. The DISCERN™ test was developed and validated to provide physicians with a test with improved sensitivity and specificity when diagnosing AD, providing them with greater confidence in the accuracy of the diagnosis and the treatments they recommend to patients. The DISCERN™ test has been validated using autopsy-confirmed cases AD, including cases with mixed dementia [11-15].

The goal of this study was to evaluate the clinical utility of DISCERN™ and assess how physicians would use this test in the real-world to inform patient diagnosis and management.

MATERIALS AND METHODS

Participant Inclusion/Exclusion

A total of 402 physicians (50 geriatricians, 102 neurologists, 250 PCPs) qualified to participate in a web-based survey study, hosted through a recruiting agency. Physicians were eligible to participate if they (1) were board-certified in neurology, geriatrics, or primary care/family medicine/internal medicine; (2) had seen more than 10 patients (PCPs, geriatricians), or 20 patients (neurologists) with suspected dementia in the past six months; (3) had evaluated more than 10 patients (PCPs, geriatricians), or 15 patients (neurologists) with suspected

dementia for AD in the past six months; (4) had any patients with suspected dementia eventually diagnosed with AD in the past six months; (5) had been practicing in their current specialty for more than 3 years and less than 35 years; (6) were actively treating the majority of their patients in an office-based private practice, community hospital, or academic medical center; (7) spent 50% or more of their time performing direct clinical care, versus administrative or clinical research duties; and (8) were currently practicing in any state of the U.S., except in Maine or Vermont (due to restrictive market research rules that do not permit compensation to participants). The physicians that completed the survey were granted an honorarium of $20 (PCPs) or $35 (neurologists, geriatricians).

DISCERN™ Test Description

Participants were provided a masked description of the DISCERN™ test (Test X) conveying the following information: the test is a novel AD diagnostic combining three biomarkers: Morphometric Imaging (measures fibroblasts ability to form networks), Protein Kinase C ε (measures synaptic growth), and AD-Index (measures phosphorylation of Erk1 and Erk2 in response to bradykinin); the test is the only AD diagnostic validated against autopsy confirmed diagnosis (NIH gold standard for AD diagnosis) with 95% sensitivity and 95% specificity; the test requires a 3 mm skin-punch biopsy and is currently offered as a laboratory developed test in a Clinical Laboratory Improvement Amendments (CLIA) certified lab; all three biomarkers from the test have been validated to accurately distinguish AD from non-AD dementias [11-14].

Conjoint Analysis Experimental Design

This study employed conjoint analysis, a technique used to assess physicians' choices regarding patient management decision-making based on individual attributes provided in discrete patient profiles, most important of them being the DISCERN™ result and results of SOC tests [16,17]. Hypothetical patient profiles were created using Sawtooth Software's Conjoint Value Analysis (CVA) module, version 3.0.[18]. These patient profiles contained attributes (patient characteristics) and levels (specific values associated with each attribute), developed through a literature review and primary research with clinical experts [7-9,19-26]. A total of five attributes were included in this study: DISCERN™ results, MRI/CT scan results, Mini-mental state examination score (MMSE) score, Blood test results, and Age (years). The levels associated with each attribute are shown in Table 2.

Table 2: Attributes and Levels Used in the Generation of Hypothetical Patient Profiles.

Attributes and Levels			
Attribute	**Level 1**	**Level 2**	**Level 3**
DISCERN™ Result	No test	Negative for AD	Positive for AD
MRI/CT scan	No presence of microhemorrhage, cerebral amyloid angiopathy, or atrophy	Presence of microhemorrhage, cerebral amyloid angiopathy, or atrophy	N/A
MMSE Score	20-24 (mild dementia)	13-19 (moderate dementia)	<=12 (severe dementia)
Blood Test Results	No TSH, vitamin B12 or folate abnormalities, Lyme disease, or syphilis	TSH, vitamin B12 or folate abnormalities, Lyme disease, or syphilis present	N/A
Age (years)	65	75	85

Table 3: Impact of DISCERN™ test results on Physician Decision-Making.

Outcome	**DISCERN™ Test Result**	**Odds Ratio**	**Confidence Interval**	
			Lower Bound	**Upper Bound**
Definitively diagnose AD	**No Test**	**REF**	-	-
	Negative for AD	0.39*	0.32	0.48
	Positive for AD	6.45*	5.09	8.17
Prescribe treatments for symptoms of cognitive impairment	**No Test**	**REF**	-	-
	Negative for AD	0.58*	0.48	0.70
	Positive for AD	2.98*	2.40	3.68
Refer to a neurologist	**No Test**	**REF**	-	-
	Negative for AD	1.07	0.86	1.33
	Positive for AD	0.97	0.78	1.20
Prescribe Drug X**	**No Test**	**REF**	-	-
	Negative for AD	0.57*	0.47	0.70
	Positive for AD	4.12*	3.36	5.04

*Significant at α =0.05; **Drug X was described to respondents as a futuristic disease-modifying drug for AD with a desirable safety and efficacy profile

After constructing the profiles, the survey design was optimized using Sawtooth Software to compute the number of profiles presented to respondents, as the full factorial design (all possible profiles) included 108 discrete profiles. By generating a balanced orthogonal design of 27 profiles, response efficiency was improved, and respondent burden was reduced. An orthogonal design includes a subset of profiles that represent the full factorial design and ensures that the attributes' levels are not correlated with each other and that each level is presented in the design an equal number of times [16]. The orthogonal design thus generated had a high D-efficiency (0.99), indicating that it closely represented the full factorial design.

Four outcomes represented physician decision-making. For each patient profile, physicians were asked to choose "yes" or "no" for the following questions: (1) Would you diagnose this patient as having AD?; (2) Would you prescribe medications indicated for cognitive impairment in AD to this patient?; (3) *[PCPs and geriatricians only]* Would you refer this patient to a neurologist?; (4) Would you prescribe a disease-modifying drug (Drug X [futuristic, hypothetical drug with a desirable safety and efficacy profile]) to this patient that slows the progression of AD?.

Data Collection

A physician survey recruiting agency hosted the web-based survey. Informed consent was obtained from all the participants/respondents to participate. The survey was self-administered and had a 15-minute response time by design (average survey time: 0:14:50 min.). Prior to launch, the survey was piloted with three physicians – a neurologist, a geriatrician, and a PCP – to validate the survey questions and clinical vignettes for readability and clinical accuracy. In the pilot, a holdout profile analysis was conducted to ensure test-retest reliability. Respondents were presented with two profiles (hold-out profiles) with identical attributes and levels, and respondents answered the same four outcome questions; for the two hold-out profiles, physicians answered identically, indicating high test-retest reliability. Feedback received during the pilot was implemented into the survey prior to launch. Launch data was collected between November 15, 2021, and December 5, 2021. The survey and the blinded product profile are displayed in the appendix. An independent Institutional Review Board (IRB) reviewed and exempted the study from full review as it lacked inclusion of any sensitive, identifiable information collected from survey participants.

Data Analysis

Data analyses were performed using Sawtooth Software. Multivariable logit analysis of dummy data produced standard errors less than 0.10 and confirmed that a sample of 400 physicians would be sufficient for this study.

Four separate multivariable logit models were used to analyze the impact of the DISCERN™ result and other attributes on the four outcomes. These models produced raw utilities, or measures of relative worth, for each level of each attribute. The impact of each attribute (relative importance of each attribute (RAI)) on physician decision-making was calculated as the mean difference in the minimum and maximum utility for each level and the proportion this makes up of all the attributes. Odds ratios and 95% confidence intervals were calculated to assess the impact of the DISCERN™ result on outcomes compared to no test.

Findings

Demographic Characteristics: In total, 1,936 invitations to the survey were sent. Of the 702 physicians who entered the survey (36% of those invited), 300 were excluded based on screening criteria and 402 ultimately qualified (invited response rate: 21%). The sample was demographically representative of the physician composition in the U.S.; 33% of physicians practice in the South, 23% each in the Northeast and West, and 22% in the Midwest [27]. Most physicians (81%) work in office-based private practices, followed by community hospitals (11%) and academic medical centers (8%).

Descriptive Findings: Overall, 48% of surveyed physicians reported that they are satisfied (44%) or extremely satisfied (4%) with current methods for assessing AD. Satisfaction among PCPs was lower (40%) than neurologists (64%); 77% of physicians cited a lack of a definitive test to diagnose AD as the greatest diagnostic challenge (n=310), followed by cost of SOC testing (56%) and high subjectivity in the interpretation of current test results (54%). Figure 1 shows other diagnostic challenges cited by physicians.

Physicians cited several benefits of more accurately and efficiently identifying AD and differentiating it from other dementias: prescribing appropriate treatment earlier in disease (n=329, 82%), avoiding inappropriate drugs in patients who do not have AD (n=308, 77%), and peace of mind for patients with a definitive diagnosis of AD (n=264, 66%). 90% of physicians indicated that they are likely to order DISCERN™, citing the following benefits: ability to aid in treatment decision-making (69%), less invasiveness compared to CSF testing (67%), high accuracy (67%), and ability to provide an objective, definitive AD diagnosis (66%).

Conjoint Analysis: A total of 388 physicians participated in the conjoint portion of the survey after 14 physicians were ruled out either for indicating that they are unlikely to order DISCERN™ (n=6) or for straight lining the conjoint responses (choosing identical responses across every profile) (n=8). Odds ratios demonstrating the association of physician decision-making with the DISCERN™ result and other independent variables were generated using an aggregate logit model (Table 3). The DISCERN™ result had a statistically significant (α=0.05) impact on all decision-making outcomes (compared to no test), aside from referral to a neurologist. A positive result was associated with significantly higher odds of physicians definitively diagnosing AD (OR: 6.45, CI: 5.09-8.17). Conversely, a negative result was associated with significantly lower odds of physicians definitively diagnosing AD (OR: 0.39, CI: 0.32-0.48). Physicians were 2.98 times more likely to prescribe treatments for symptoms of suspected dementia with a positive DISCERN™ result (CI: 2.40-3.68). A positive DISCERN™ result was associated with significantly higher odds of physicians prescribing a disease-modifying drug (OR: 4.12, CI: 3.36-5.04). Physician decision-making for referring to a neurologist was not significantly impacted by any result from DISCERN™.

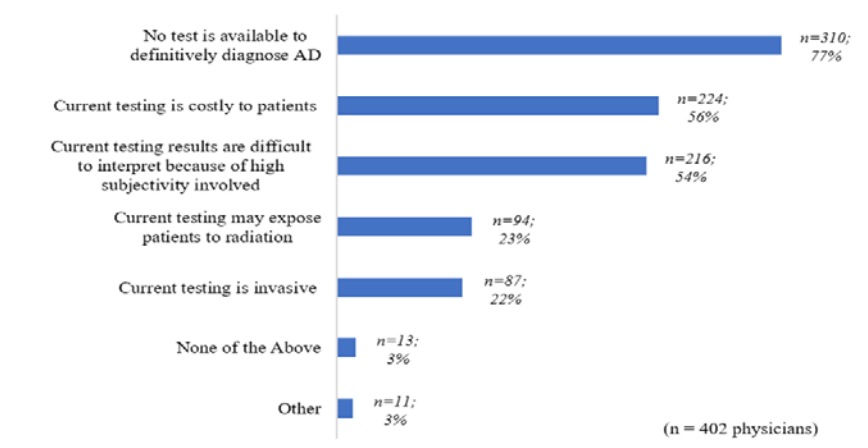

Figure 1 Current Diagnostic Challenges Pertaining to Alzheimer's Disease.

The DISCERN™ result consistently ranked as the most important attribute in physician decision-making regarding diagnosis and management of patients with suspected dementia (Figure 2). The DISCERN™ result was the most important attribute for physicians when definitively diagnosing AD (relative attribute importance (RAI): 64%), followed by the MMSE score (RAI: 14%). It was also the most important attribute for physicians when prescribing a futuristic, hypothetical disease-modifying drug (RAI: 62%), followed by MMSE score (RAI: 15%). Physicians found the DISCERN™ result as the most important attribute in decision-making when prescribing treatments for symptoms of cognitive impairment (RAI: 54%), followed by MMSE score (RAI: 19%). Finally, the model demonstrated that the most important attribute in geriatricians' and PCPs' decision to refer a patient to a neurologist was a patients' MMSE score (RAI: 48%), followed by age (RAI: 19%).

Relative attribute importance by physician type was calculated from Hierarchical Bayesian models (not shown in Figure 2). Interestingly, neurologists ranked the DISCERN™ result as a more important attribute in decision-making for prescribing treatments for symptoms of suspected dementia compared to PCPs and geriatricians (RAI: 54%, 47%, and 45%, respectively). PCPs, neurologists, and geriatricians ranked the DISCERN™ test as the most important attribute equally when diagnosing AD (RAI: 55%, 55%, and 54%, respectively). PCPs, neurologists, and geriatricians also consistently ranked the DISCERN™ test as the most important attribute for prescribing a futuristic disease-modifying therapy (RAI:53%, 53%, and 51%). Geriatricians ranked DISCERN™ as the most important attribute in referring to a neurologist (RAI: 29%), whereas MMSE score was the most important attribute for that of PCPs (RAI: 30%).

DISCUSSION

This decision-impact study demonstrates that physicians identify several unmet needs associated with currently available diagnostic tests used to evaluate patients with symptoms of suspected dementia and a majority indicate that they will use the DISCERN™ test in patient evaluation and management. Physicians place greater importance on the DISCERN™ result than on MRI/CT scan results, MMSE score, blood test results, and age when diagnosing AD, prescribing treatments for symptoms of suspected dementia, and prescribing a futuristic disease-modifying drug with a desirable safety and efficacy profile.

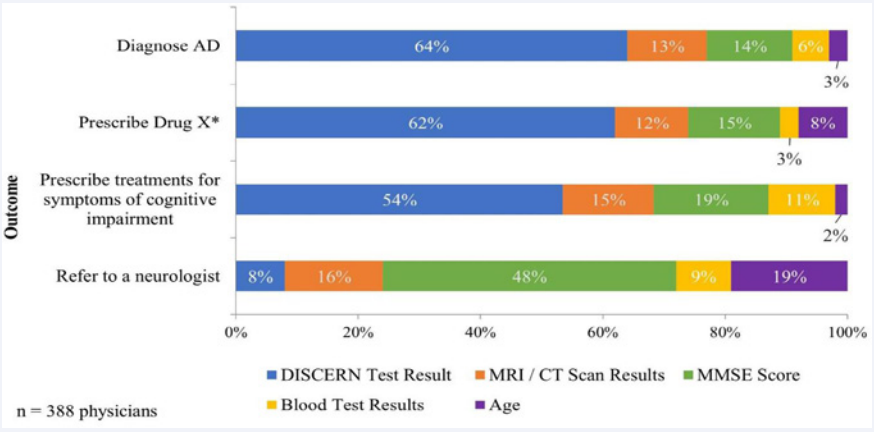

Figure 2 Relative Importance of DISCERN™ Results Compared to Other Test Results and Clinical Variables.
*Drug X was described to respondents as a futuristic disease-modifying drug for AD with a desirable safety and efficacy profile

Except for "referring a patient to a neurologist", the DISCERN™ result has a statistically significant impact on all decision-making outcomes, compared to no test.

The clinical utility of a diagnostic is defined as the extent to which the result of the test is associated with actionable decision-making that can have an impact on health outcomes. As the only objective test to rule-in AD, the DISCERN™ test demonstrates clinical utility in reducing uncertainty associated with AD diagnosis present with other diagnostic modalities. Physicians indicate using DISCERN™ results to make prescribing decisions. Several studies found evidence to suggest that acetylcholinesterase inhibitors and NMDA inhibitors stabilize or improve cognitive function and global status in patients with AD [28,29]. DISCERN™ can also improve patient outcomes by facilitating appropriate treatment selection. In 2021, the FDA approved aducanumab (Aduhelm™), for use in treating patients with mild dementia due to AD; several additional disease-modifying drugs are currently in development pipelines [30,31]. With the discovery and approval of future therapies, AD diagnostic tests with high sensitivity and specificity for early-stage disease will become increasingly important to enable proper initiation of therapy. Physicians would use the DISCERN™ test to inform prescribing decisions regarding these therapies, especially since the potentially high cost of and safety-monitoring considerations for these therapies will likely require a definitive AD diagnosis.

Our study has five noteworthy findings with implications for several key stakeholders. First, our study documents that there are several unmet needs in current diagnostic tests for AD as identified by physicians. The DISCERN™ test will address several unmet needs and allow physicians to objectively diagnose AD with minimal invasiveness, while offering patients and caregivers greater certainty in their diagnosis, thereby facilitating future care planning. Second, our study confirms that, compared to current SOC tests, the DISCERN™ result is more important to inform physician decision-making related to diagnosis and treatment planning. Physicians clearly indicate that they have greater confidence in the DISCERN™ test and will use it to better manage patients, make more informed treatment decisions, and positively impact patient outcomes. Third, compared to no test, a positive DISCERN™ result was associated with significantly higher odds of diagnosing AD, prescribing appropriate treatments for suspected dementia, and prescribing a futuristic disease-modifying drug with an acceptable safety and efficacy profile. Conversely, compared to no test, a negative DISCERN™ result was associated with significantly lower odds of diagnosing AD and prescribing treatments. This indicates that physicians would use the positive result to rule-in patients while a negative result would be used to rule-out patients with greater confidence than when the test is unavailable. Fourth, the decision impact of the DISCERN™ result on treatment decisions is not only acknowledged by PCPs and geriatricians, but also by neurologists, even though a greater proportion of neurologists are satisfied with current tests (64%) compared to PCPs (40%) and geriatricians (50%). This indicates that there is a broadly accepted need for an improved test in the diagnostic pathway for AD, irrespective of physician specialty. Lastly, the DISCERN™ result would not generally impact PCPs' and geriatricians' decision to refer to a neurologist, possibly because this decision is independent of a definitive AD diagnosis. Referral to a neurologist to further manage symptoms of AD was not a clearly identified value of accurately and efficiently identifying AD. The role of neurologists in the disease management pathway is likely more upstream and the DISCERN™ test could be used by neurologists alongside neurological evaluations to diagnose a patient with AD.

Conclusions, Limitations, & Recommendations

The survey results confirm that physicians see value in the results from the DISCERN™ test to make clinical decisions compared to current SOC tests. This study documents the clinical utility of the DISCERN™ test in addressing current unmet needs in AD diagnosis and management.

This study has several limitations to consider. First, while comprehensive, our study was not performed in a real-world setting and thus left room for potential biases that could not be measured directly or controlled for, although we note that the profiles were randomly assigned to participants and believe this risk is relatively low. The study asked physicians to assume that test cost and insurance coverage were not issues, so the impact of these factors on physician decision-making was not examined; however, in practice, these two factors are likely to have an impact on the usage of any diagnostic test (including PET scan, MRI, and potentially the DISCERN™ test). The results of this study should be interpreted considering this limitation. Second, the hypothetical patient profiles were limited to the most important clinical variables to create a viable choice experiment. Physicians may rely on additional clinical information not presented when diagnosing and managing AD patients. However, since these profiles were based on a literature review and validated through primary research with practicing clinicians, we believe they closely represent the most relevant factors considered in the real-world. Lastly, this study used a survey to assess physician behavior rather than observing it in the real-world. While traditional self-report surveys may be subject to social desirability bias, our study uses a preference elicitation technique that closely mimics the real-world [16]. Also, high test-retest reliability was observed in the pretest, which increases our confidence in the study result.

Based on the results of this study, we believe that the DISCERN™ test will be adopted broadly by clinicians as part of the future diagnostic pathway for evaluating patients with cognitive impairment suggestive of AD and it will have a significant positive impact on patients, their caregivers, and society. Based on the analytical validity, clinical validity, and clinical utility of the DISCERN™ test demonstrated through the extensive research presented in this report, we believe that physicians and patients should have routine access to the test when its use is clinically indicated.

DECLARATIONS

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Authors' Contributions

MD, NM, and CS contributed equally to study design, review,

analysis, and interpretation of study data, and manuscript development. SH and FH contributed equally to study design, review and interpretation of study data, and manuscript development. TG contributed to study design, review and interpretation of study data, and manuscript development. All authors read and approved the final manuscript.

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